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Interview

30 years of PI3K: an interview with Bart Vanhaesebroeck

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"I think myself extremely lucky to be in an environment where we have the freedom to explore new ideas and, with a bit of luck and hard work, help to alleviate some human diseases"

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Could you please introduce yourself & provide a brief summary of your career to date?

Many thanks for this interview – my answers below are targeted at a wider nonspecialist audience.

I am a basic scientist with a keen interest in applying newly acquired knowledge to understand and treat human disease. Throughout my research career, I have always been involved in fundamental research that could be applied to drug development. I have had the pleasure that some of our discoveries have made it all the way to approved drugs for leukemia.

Following training in Biology/Biochemistry, I obtained a PhD in a laboratory in Belgium that was among the first to clone human genes to produce so-called recombinant proteins. This was in the early days of molecular biology, when scientists like Walter Fiers, my PhD mentor, were looking to exploit DNA technology to produce large amounts of 'natural' products from the human body to use as medicines, such as insulin to activate metabolism or natural immune stimulators. This was the beginning of the biotech industry, which at the time spawned companies such as Biogen and Genentech. Doing a PhD in an environment where research was being applied in so-called translational research was a huge privilege and shaped my thinking on how I wanted to do future research.

My PhD studies focused on investigating the basic biology of some of these recombinant proteins such as Tumour Necrosis Factor and Interleukin-2. This also meant that when I finished my PhD, I had not yet had a chance to clone a gene myself. I subsequently picked up these skills in my postdoctoral lab at the Ludwig Institute for Cancer Research in London where my colleagues and I cloned genes for so-called PI 3-kinases (PI3Ks), an area I have been working in for over 30 years now.

PI3Ks control cell behavior and are involved in many different types of diseases, in particular cancer and immune deregulation. With my laboratory and our collaborators, we made a new type of mouse model to uncover the functions of these PI3Ks in the organism. This allowed us to publish impactful papers, but also to identify some PI3K family members as new drug targets. Together with studies from other laboratories, these findings led to extensive development efforts of PI3K inhibitor drugs. It was great to see how others also saw the potential therapeutic application of our findings, and it was an interesting experience for my laboratory to become involved in drug development, something I really enjoyed. Drugs against some PI3Ks are now approved for cancer and PI3K-associated rare diseases.

Not every discovery you make in science is easily translatable to drug development. I intentionally picked this type of 'druggable' research subject because I wanted to eventually apply our scientific discoveries. Over the years, I have been fortunate enough to find myself in the space between basic scientists, technologists, drug developers and clinicians, and learning to speak the different languages used in these sectors and to understand their specific challenges.

Some of our discoveries have led to the development and eventual approval of drugs, something I am very proud of.

For the benefit of our patient & non-scientific readers, could you please give a brief overview of the PI3K pathway & emphasize its importance in cancer research?

We are all made up of cells, and cells respond to their environment. Information from the outside must be relayed to the inside of the cell to execute specific functions. PI3K is one of these so-called signal transducers. Proteins like these organize 'signal transduction pathways' in the cell, which are a bit like the metro networks in a large town which allow you to go to from one place to another. PI3K is a very important underground metro station that you often must travel through and is therefore a key player in cells.

In the case of PI3K, there are eight family members which perform different functions in cells. To find out what each of the PI3K family members is doing in cells and in the organism has kept us busy for about 20 years. Interestingly, it turns out it is possible to make drugs against every PI3K family member. As we will explain in more detail below, we think it is also possible to make activators of each PI3K.

Cancer cells 'hijack' PI3K to switch on signals in cells without a normal signal coming from the outside. Cancer cells use PI3K to become a bit like self-starters, something that we try to block with drugs. PI3Ks can also become over-stimulated in the immune system, and inhibitors have been developed to block that response. Somewhat counter-intuitively, inhibitors against PI3Ks that are expressed in white blood cells can rebalance the immune system to induce an anti-cancer immune response. These inhibitors are currently being tested in so-called cancer immunotherapy.

I've really enjoyed your use of analogies throughout your talk today & in your explanations of the role of PI3K within the cell. Could you tell us more about those?

Yes, in my experience, simple analogies are often the only thing that people remember from scientific talks. I use this also in daily life, somewhat to the frustration of my now grown-up children.

In fact, my daughter came up with an analogy which I now use to describe some key aspects of our ongoing research. This revolves around the question whether in cancer, one needs to activate or inhibit PI3K to kill cancer cells. My daughter compared a cancer cell with a balloon full of air. PI3K inhibitors/blockers are squeezing the air out of the balloon and make it go floppy but the balloon does not pop. When the time is right, the balloon can be inflated again, similar to when cancer returns after some time. In contrast, if you put 10% more air in a fully-blown balloon, it will pop and it will never be possible to blow up the balloon again, and the cancer will not come back. Therefore, one should activate PI3K rather than inhibit it to kill cancer cells, something we are currently exploring in the lab, as explained further below.

I always tell my staff to try to use simple language to explain their science, similar to 'Children's BBC'. In these programs, concepts are presented factually correct but simplified to the core, using simple analogies. This is actually very challenging for most scientists. What is the concept? What are you trying to do?

Talking at lab tours to non-scientifically-trained visitors such as sponsors and patients is a really good exercise. For example, when someone in the lab is showing how to 'genotype mice', this is looking at the offspring of mouse A bred to mouse B and looking which genes the pups have inherited. This is in fact the same as a 'maternity/paternity' test, something people can relate to. We often, jokingly, propose for the visitors to give us some DNA to see if they are related to each other. People giggle at this but suddenly see the practical application of the rather complicated lab stuff they are being shown. Scientists should do more of this because it's important to communicate your science without saying the wrong thing. This is not the same as dumbing things down. We should also remember that we have a duty to explain our science and methods – ultimately most of the research is paid for by donations from the public and the taxpayer!

Could you please describe the projects that you & your team are currently undertaking at UCL?

Our research covers three main strands. The first is basic research – there is still a lot unknown about PI3Ks, for example what's happening in cells when PI3K is mutated such as in cancer.

We are also testing whether PI3K inhibitors, when given at low doses, can prevent or stop cancer from developing. This can be of specific importance in hereditary cancers where the risk of cancer development is well-known. The idea is to keep cancer at bay, winning time before the cancer develops. For these studies, we use genetically-modified mice which carry the same mutations as in humans, resulting in the development of different cancer types within a year. Our preliminary data look promising, with some well-tolerated drugs able to prevent cancer and extend life in mice. It is hoped that similar approaches will one day be possible in the wider human population.

After having inhibited PI3Ks for over 30 years, we are now also exploring whether we can activate PI3K using small molecules. PI3Ks do a lot of good things in the body, and the idea is to test whether we can harness this by activating PI3K for short periods of time when needed. This can be useful in tissue regeneration such as wound healing and diabetic wounds and nerve regeneration. We have just published a paper in *Nature* on this concept. We have good indications that a PI3K activator can be used to make nerves regenerate faster, something we are trying to develop further in a spin-out company for which we are currently seeking investment. We are also exploring if PI3K activation could be used to stimulate the immune response (for example during vaccination). Paradoxically, short-term overactivation of PI3K could also be useful in killing cancer cells, as explained above with my daughter's balloon analogy. The idea here is to over-stimulate cancer which is already under stress. This is probably one of our most controversial ideas, and I hope to be able to secure funding to explore this further – it is definitely a new modality to interfere with cancer!

I think myself extremely lucky to be in an environment where we have the freedom to explore new ideas and, with a bit of luck and hard work, help to alleviate some human diseases.

In September 2023, you organized a Biochemical Society Meeting on PI3K pathway. What were some of the highlights of this meeting & do you plan to organize similar events in future?

This oversubscribed meeting clearly illustrated renewed interest in PI3K. Scientific discovery and drug development go in waves – this also applies to PI3K research and development which has gone through a dip over the last couple of years, following disappointing outcomes of clinical trials with first generation PI3K inhibitors. In the early days of PI3K, clinical expectations were somewhat inflated, with massive drug development before the pathway was properly understood. The highlights at the meeting were that we now understand the PI3K pathway and its challenges and pitfalls for clinical application much better. It was hugely interesting to see basic scientists, clinicians, drug developers and patients interacting at the meeting. We organized a session with patients which was really inspiring. For example, we had a 16-year-old boy explaining his diagnosis of a PI3K-associated rare disease, what the challenges are and how PI3K drugs have helped him.

Our Barcelona meeting clearly illustrated the momentum to organize a follow-on PI3K meeting in the near future. It would also be great to link up PI3K with some other signal transduction pathways, there is a risk for research to end up in so-called 'silos' – cancer for example is a hugely complicated disease which need to be attacked from all angles.

What are the challenges to developing novel therapeutics based on the PI3K pathway & how do you think they could be overcome?

The most important aspect in my view is to follow the science. When PI3Ks were first discovered, this generated enormous interest, given that these enzymes are over-active in cancer and immune malfunctions but importantly, could also be targeted by small molecules. This created a rush and high expectations which were not always in line with the basic findings on PI3Ks. The fact is that the biology and science will always eventually show up in the clinic, and it is better to be prepared for what could come. Examples are serious side effects of PI3K drugs on metabolism, side effects such as colitis and the toxicity of blocking many PI3K family members at once. Having said this, it is worth trying some of these avenues in challenging diseases such as cancer, as one cannot really predict how drugs will work in the clinic. We now better understand the PI3K pathway and now know what (not) to do.

Another big challenge is to convince investors to come back to the field – there is some reluctance not only because of previous negative experience in the PI3K inhibitor field, but also because the regulatory landscape has changed, with PI3K having been singled out in high-profile US FDA reports as a troublesome field, for which more complex clinical trials are now requested. This is a huge challenge for some cancer types for which there are not many patients but also from a return-on-investment perspective.

Do you have any colleagues that you look up to or are inspired by? Did you have any role models as a student or in your early career?

As a group, I greatly admire my clinical colleagues who perform research. This is a challenging and demanding combination, both from a personal and logistic perspective. It must not always be easy to switch from difficult clinical sessions with cancer patients to lab research, where people might be complaining about relatively small problems compared with what some of these patients must go through.

As individual role models, I often refer to Walter Fiers, my PhD supervisor mentioned earlier. He was an agricultural engineer who applied his biochemical knowledge from the brewing industry to make natural medicines, exploiting new technologies in molecular biology that he helped to develop. The same applied to the laboratory next door, led by Marc Van Montagu and Jeff Shell, who invented ways to make plants take up genes, for example to make rice that contains added vitamins, or are resistant to pests. These people were pioneers in their field and often had to work under difficult financial circumstances in Belgium. Toward the end of their careers, the Flemish government began to appreciate their work and that of other pioneers in Belgium and set up the Flemish Institute for Biotechnology (VIB), a hugely successful inter-university organization which produces some of the best in fundamental science but is at the same time very applied and translational. Many of my friends and colleagues are still there, they are doing the same thing as me, but on a much larger scale. I hugely admire people like Walter Fiers and Van Montagu for their vision and foresight, the opportunities they gave to people and their perseverance and vision. We need more of those!

Interview disclosure

The opinions expressed in this interview are those of B Vanhaesebroeck and do not necessarily reflect the views of Taylor and Francis.

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Competing interests disclosure

B Vanhaesebroeck is a consultant for iOnctura (Geneva, Switzerland) and Pharming (Leiden, the Netherlands) and a shareholder of Open Orphan (Dublin, Ireland). The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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